Remarks

Claims 18-32 are pending in the presesnt application, however claims 18-26 have been withdrawn pursuant to a restriction requirement. Claims 18-26 are canceled herein, without prejudice to prosecution of this subject matter in a divisional application. Claim 32 also is canceled herein.

The Examiner has indicated that the Alberto et al. reference, which is of record in the application file of parent application Serial No. 09/576,960, is not available in the files of the United States Patent and Trademark Office and therefore has not been considered by the Examiner in this case. Applicants enclose a copy of this reference for the Examiner's consideration in the accompanying Supplemental Information Disclosure Statement. Applicants also request consideration of the reference and written confirmation of such consideration at this time.

Claims 27-32 are rejected under 35 U.S.C. §112, second paragraph, as indefinite. The Office has objected to the terms "including," "may be" and "discrete molecule" in claim 27. Applicants have amended this claim to avoid use of these terms. In addition, this claim has been amended for the sake of clarity with respect to the components of the lyophilized stannous ion formulation. Applicants therefore respectfully submit that the claims now fully comply with the standards for definiteness of 35 U.S.C. §112, second paragraph, and request that the Office withdraw the rejection of this claim on this basis.

The Office has objected to the term "gluceptate," which is found in claim 30, as a term not well known in the art.

Applicants traverse the rejection of claim 30 on this ground. Gluceptate is a term well-known by those skilled in arts pertaining to drug and imaging agent formulations as synonymous with glucoheptonate. The term glucoheptonate also is used in the specification, for example at page 8, line 19. Enclosed for the reference of the Office is a copy of the entry in Dorland's Medical Dictionary (on-line), which defines the term as the USAN contraction for glucoheptonate. The Merck Index (2001), which also is enclosed, also refers to "gluceptate" in the entry for glucoheptonate. This evidence demonstrates that this term is not unclear or unknown to persons skilled in the relevant art. Applicants request that the Office withdraw this rejection since a skilled person would have no difficulty in understanding the claim due to use of the term "gluceptate."

The Office has objected to the phrase "multidentate aminopolycarboxylate ligand" in claim 31 as unclear. Claim 31 has been amended for clarity and to avoid the term "multidentate." Applicants submit that claim 31 complies with the standards of 35 U.S.C. §112, second paragraph and request that the rejection of claim 31 on this basis be withdrawn.

Claims 27-32 are rejected under 35 U.S.C. §112, first paragraph, assertedly for lack of sufficient description to support the phrase "discrete molecule." Applicants have amended claim 27 for reasons of readability and clarity, and have deleted the term objected to by the Office. Applicants therefore request the rejection on this basis be withdrawn.

Claims 27-28 are rejected under 35 U.S.C. §102 as anticipated by Azuma et al. and by Adler et al. These references

are cited by the Office as each describing a kit which comprises lyophilized stannous ion in combination with radioactive technetium. Claim 27 has been amended to specifically recite a kit comprising (1) a lyophilized stannous ion formulation which comprises said stannous ion and an anion, (2) carbon monoxide and (3) a metal M selected from the group consisting of Mn, ^{99m}Tc, ^{186}Re and ^{188}Re. Support for the amendment may be found in the specification as originally filed at, for example, page 5, lines 18-19 and 21-23, page 8, lines 21-22 and 25-28, page 9, lines 14-15 and original claim 18. The Office is required to show that the cited reference contains, within its four corners, all elements of the rejected claim to make out a proper case for anticipation. Applicants submit that neither the Adler et al. nor the Azuma et al. reference teaches, suggests, or even refers to carbon monoxide and does not, therefore, contain all elements of the claims as amended. Applicants respectfully submit that the amendment obviates the rejection and request that it be withdrawn.

Claims 30 and 31-32 are rejected under 35 U.S.C. §102 as anticipated by Adler et al., which assertedly discloses a kit which comprises stannous ion, a gluceptate salt, radioactive technetium and a multidentate ligand. All of claims 30 and 31-32 are dependent from claim 27, which has been amended to recite carbon monoxide. Applicants respectfully submit that the amendment to claim 27 overcomes these rejections for the reasons discussed above with respect to the rejection of claims 27 and 28. The Adler et al. reference does not mention carbon monoxide and therefore does not teach or even suggest this required claim element. Because the reference does not contain within its teachings all elements of the rejected claim, rejection of this

amended claim as anticipated is not proper. Applicants therefore request that this rejection be withdrawn.

Claims 27-29 are rejected under 35 U.S.C. §102 as anticipated by Mallinckrodt (WO 96/30054), which assertedly discloses a kit which comprises a lyophilized stannous ion in combination with radioactive technetium and lactose. Amended claim 27 recites a kit which comprises carbon monoxide. Applicants respectfully submit that this feature distinguishes the claims from the disclosures of the Mallinckrodt reference. This reference therefore does not anticipate the rejected claims. Applicants therefore request that the Office withdraw this rejection of claims 27-29.

For the foregoing reasons, Applicants request that the Office withdraw all rejections and reconsider the claims of this application.

Respectfully submitted,

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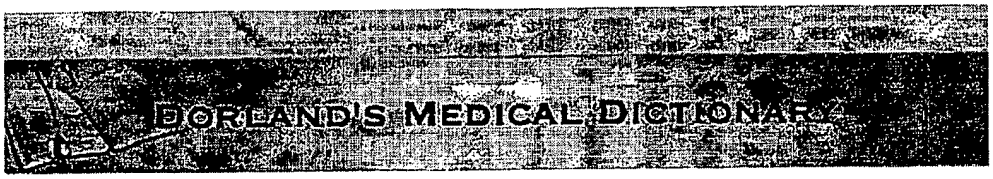

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G

glossocoma — glucuronide

glossocoma (glos·soc·o·ma) (glos-ok'o-m[schwa]) retraction of the tongue.

glossodynamometer (glos·so·dy·na·mom·e·ter) (glos"o-di"n[schwa]-mom'[schwa]-t[schwa]r) [*glosso-* + *dynamometer*] an instrument for recording the power of the tongue to resist pressure.

glossodynia (glos·so·dyn·ia) (glos"o-din'e-[schwa]) [*glosso-* + *-odynia*] glossalgia.

glossodynia exfoliati'va, Moeller's glossitis.

psychogenic glossodynia, glossopyrosis.

glossoepiglottic (glos·so·epi·glot·tic) (glos"o-ep-[ibreve]-glot'ik) glossoepiglottidean.

glossoepiglottidean (glos·so·epi·glot·tid·e·an) (glos"o-ep-[ibreve]-glo-tid'e-[schwa]n) pertaining to the tongue and epiglottis.

glossograph (glos·so·graph) (glos'o-graf) [*glosso-* + *-graph*] an apparatus for recording the tongue movements in speech.

glossohyal (glos·so·hy·al) (glos"o-hi'[schwa]l) [*glosso-* + *hyoid*] pertaining to the tongue and hyoid bone.

glossokinesthetic (glos·so·kin·es·thet·ic) (glos"o-kin"[schwa]s-thet'ik) [*glosso-* + *kinesthetic*] pertaining to the subjective perception of the movements of the tongue in speech.

glossolalia (glos·so·la·lia) (glos"o-la'le-[schwa]) [*glosso-* + *lal-* + *-ia*] speech in

secreted by the alpha cells of the islets of Langerhans in response to hypoglycemia, acetylcholine, some amino acids, and growth hormone; it stimulates glycogenolysis in the liver by activating liver phosphorylase and promotes gluconeogenesis and ketogenesis and stimulates the release of insulin by the pancreatic islets. Called also *hyperglycemic-glycogenolytic factor*. 2. a preparation of this hormone obtained from the organs of slaughtered food animals; administered by injection.

gut glucagon, enteroglucagon.

glucagonoma (glu·ca·gon·o·ma) (gloo"k[schwa]-gon-o'm[schwa]) a type of islet cell tumor of the alpha cells that secretes glucagon; some are malignant. See also *glucagonoma syndrome*, under *syndrome*.

glucal (glu·cal) (gloo'kal) a glycal of glucose.

glucan (glu·can) (gloo'kan) any polysaccharide (e.g., glycogen, starch, and cellulose) composed only of recurring units of glucose; a homopolymer of glucose.

1,4-α-glucan branching enzyme (1,4-α-glu·can branch·ing en·zyme) (gloo'kan branch'ing en'z[imacr]m) [EC 2.4.1.18] an enzyme of the transferase class that catalyzes the cleavage of internal α-1,4-glucoside linkages in glycogen (or, in plants, amylopectin) and transfer of the fragments into α-1,6 linkages, thus creating branches in the glycogen molecule. Deficiency of the enzyme, an autosomal recessive trait, results in glycogen storage disease, type IV. Called also *brancher* or *branching enzyme*.

glucan 1,4-α-glucosidase (glu·can 1,4-α-glu·co·si·dase) (gloo'kan gloo-ko's[ibreve]-d[amacr]s) [EC 3.2.1.3] a lysosomal enzyme of the hydrolase class that catalyzes the cleavage of glucose residues from polyglucoside chains by hydrolyzing terminal α-1,4 or α-1,6 bonds; the enzyme degrades glycogen to glucose in the lysosomes. Deficiency or absence of enzyme activity, an autosomal recessive trait, results in glycogen storage disease, type II. Called also *acid maltase* and *lysosomal α-glucosidase*.

glucan transferase (glu·can trans·fer·ase) (gloo'kan trans'f[schwa]r-[amacr]s) an enzyme transferring glucosyl chains in glucans from one site to another, usually with specific conformations of donor and acceptor sites; see *oligo-1,4,-1,4-glucantransferase* and *1,4-α-glucan branching enzyme*.

glucaric acid (glu·car·ic ac·id) (gloo-kar'ik) the aldaric acid resulting from oxidation of glucose.

gluceptate (glu·cep·tate) (gloo-sep't[amacr]t) USAN contraction for *glucoheptonate*. See also table at *technetium*.

gluciphore (glu·ci·phore) (gloo's[ibreve]-for) glucophore.

glucitol (glu·ci·tol) (gloo's[ibreve]-tol) sorbitol.

gluc(o)- (gluc(o)-) [Gr. *glykys* sweet] a combining form denoting relationship to sweetness, or to glucose. Cf. *glyc(o)-*.

glucoamylase (glu·co·am·y·lase) (gloo"ko-am'[schwa]-l[amacr]s) glucan 1,4-α-glucosidase.

glucoascorbic acid (glu·co·ascor·bic ac·id) (gloo″ko-[schwa]-skor′bik) a seven-carbon homologue of ascorbic acid having no vitamin C activity.

glucocerebrosidase (glu·co·cer·e·bro·si·dase) (gloo″ko-ser″[schwa]-bro-si′d [amacr]s) glucosylceramidase.

glucocerebroside (glu·co·cer·e·bro·side) (gloo″ko-ser′[schwa]-bro-s[imacr] d″) any of the cerebrosides in which the monosaccharide head group is glucose; they occur mostly in nonneuronal tissue and accumulate abnormally in Gaucher's disease. Called also *glucosylceramide*.

glucocinin (glu·co·cin·in) (gloo″ko-sin′in) glucokinin.

glucocorticoid (glu·co·cor·ti·coid) (gloo″ko-kor′t[ibreve]-koid) 1. any of the corticosteroids (steroids produced by the adrenal cortex) that regulate carbohydrate, lipid, and protein metabolism and inhibit the release of adrenocorticotropic hormone. They also affect muscle tone and the microcirculation, participate in the maintenance of arterial blood pressure, increase gastric secretion, alter connective tissue response to injury, impede cartilage production, inhibit inflammatory, allergic, and immunologic responses, invoke shrinkage of lymphatic tissue, reduce the number of circulating lymphocytes, and affect the functions of the central nervous system. Some exert varying degrees of mineralocorticoid activity. In humans the most important ones are cortisol, cortisone, and corticosterone. Cf. *mineralocorticoid*. 2. of, pertaining to, having the properties or effects of, or resembling one of these substances.

Gluco-Ferrum (Glu·co-Fer·rum) (gloo″ko-fer′[schwa]m) trademark for preparations of ferrous gluconate.

glucofuranose (glu·co·fu·ra·nose) (gloo″ko-fu′r[schwa]-n[omacr]s) glucose occurring in the cyclic furanose configuration; it is a minor constituent of glucose solutions.

glucogenesis (glu·co·gen·e·sis) (gloo″ko-jen′[schwa]-sis) [*gluco-* + *-genesis*] the formation of glucose from any of the products of glycolysis.

glucogenic (glu·co·gen·ic) (gloo″ko-jen′ik) [*gluco-* + *-genic*] giving rise to or producing glucose.

glucohemia (glu·co·he·mia) (gloo″ko-he′me-[schwa]) glycemia.

glucoheptonate (glu·co·hep·to·nate) (gloo″ko-hep′t[schwa]-n[amacr]t) GHA; a seven-carbon carbohydrate derivative; complexed with technetium 99m it is used in renal and brain imaging and in dynamic renal and cerebral perfusion studies. See table at *technetium*. Called also *gluceptate* (USAN contraction).

THE
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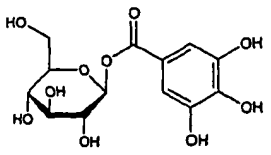
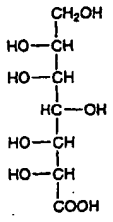


Bitter microscopic prisms from water, methanol or 80% ethanol, mp 207°. $[\alpha]_D^{25}$ −24.5° (c = 1.75 in water). Freely sol in hot water. Sparingly sol in cold water, methanol, ethanol, acetone, ethyl acetate. Practically insol in ether, benzene, chloroform, petr ether.

4468. Glucoheptonic Acid. [87-74-1] D-*glycero*-D-*gulo*-Heptonic acid; α-glucoheptonic acid; glucosemonocarboxylic acid; glucomonocarbonic acid. $C_7H_{14}O_8$; mol wt 226.18. C 37.17%, H 6.24%, O 56.59%. Obtained by treating glucose with HCN yielding a cyanohydrin which is saponified to glucoheptonic acid: Kiliani, *Ber.* **19**, 769 (1886); Fischer, *Ann.* **270**, 71 (1892); Armestar, *C.A.* **45**, 2865 (1951). Process starting with calcium cyanide and glucose: Clevenot, US **2735866** (1956 to Lab. Clevenot). Diagnostic use of ^{99m}Tc complexes in renal scintigraphy: R. E. Boyd *et al., Brit. J. Radiol.* **46**, 604 (1973); in brain scanning: J. Léveillé *et al., J. Nucl. Med.* **18**, 957 (1977); T. W. Ryerson *et al., Radiology* **127**, 429 (1978). Subacute toxicity study: L. Belbeck *et al., Can. J. Comp. Med.* **45**, 299 (1981).



Lactonizes upon evapn. The lactone forms large sweetish crystals, mp 145-148°. $[\alpha]_D^{20}$ −56.0° (shows mutarotation). Sol in water.

Sodium salt. [13007-85-7] Gluceptate sodium; sodium glucoheptonate. $C_7H_{13}NaO_8$. Prepn from corn syrup: Behnke, US **3022343** (1962 to Pfanstiehl Labs). Crystals (α-form), dec 161°. $[\alpha]_D^{20}$ +6.06° (c = 10 in H_2O). Freely sol in water.

Calcium salt. Gluceptate calcium; calcium glucoheptonate; calcium glucosemonocarbonate; calcium glucomonocarbonate; Calciforte; Calheptose. $C_{14}H_{26}CaO_{16}$; mol wt 490.42. Prepn from Na salt: Holstein, US **3033900** (1962 to Pfanstiehl Labs.). Hygroscopic crystals, somewhat acrid taste, dec 200°. Sol in water.

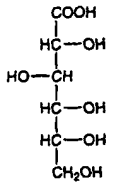
Magnesium salt. Magnesium glucoheptonate; magnesium glucosemonocarbonate; magnesium glucomonocarbonate; Navolin. $C_{14}H_{26}MgO_{16}$; mol wt 474.65. Prepn: Cipelli, US **3063896** (1962 to Merck & Co.). Water-sol crystals, pleasant taste.

Complex with ^{99m}Tc. ^{99m}Tc gluceptate; ^{99m}Tc gluheptonate; Glucoscan; TechneScan gluceptate.

USE: Pharmaceutic aid.

THERAP CAT: ^{99m}Tc complex as diagnostic aid (radioactive imaging agent).

4469. Gluconic Acid. [526-95-4] D-Gluconic acid; dextronic acid; maltonic acid; glyconic acid; glycogenic acid; pentahydroxycaproic acid. $C_6H_{12}O_7$; mol wt 196.15. C 36.74%, H 6.17%, O 57.10%. Prepd by oxidation of glucose: H. Hlasiwetz, J. Habermann, *Ann.* **155**, 120 (1870); J. Habermann, *ibid.* **162**, 297 (1872). Fermentative prepn using *Aspergillus niger*: K. Bernhauer, L. Schulof, US **1849053** (1932 to Pfizer); A. J. Moyer *et al., Ind. Eng. Chem.* **32**, 1379 (1940). Review of prepns and uses: F. J. Prescott *et al., ibid.* **45**, 338 (1953); M. Roehr *et al.* in *Biotechnology*; Vol. 6, H. Rehm, G. Reed, Eds. (VCH, Weinheim, 2nd ed, 1996) pp 347-362. *See also* Gluconolactone.



Crystals, mp 131°. Mild acid taste. $[\alpha]_D^{20}$ −6.7° (c = 1). pK (25°) 3.60. Freely sol in water, slightly sol in alcohol. Insol in ether and most other organic solvents. In aq solns the acid is partially transformed into an equilibrium mixt with gamma and delta gluconolactones.

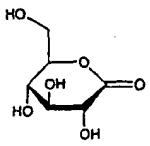
Magnesium salt. [3632-91-5] Magnesium gluconate; Almora; Ultra-Mg. $C_{12}H_{22}MgO_{14}$; mol wt 414.60. Clinical pharmacokinetics and use as magnesium supplement: J. White *et al., Clin. Ther.* **14**, 678 (1992). Also occurs as the dihydrate. Sol in water, slightly sol in alcohol. Insol in ether.

Zinc complex. [4468-02-4] (*T-4*)-Bis-(D-gluconato-κO^1,-κO^2)zinc; zinc gluconate; Rubozinc. $C_{12}H_{22}O_{14}Zn$; mol wt 455.73. Review of clinical use in treatment of colds: M. L. Garland, K. O. Hagmeyer, *Ann. Pharmacother.* **32**, 63-69 (1998). Clinical trial in inflammatory acne: J. Meynadier, *Eur. J. Dermatol.* **10**, 269 (2000).

USE: Chelating agent. In high alkalinity bottle washes and other cleansers; in finish removers; in the tanning and textile industry.

THERAP CAT: Magnesium salt as magnesium replenisher; zinc complex as zinc supplement.

4470. Gluconolactone. [90-80-2] D-Gluconic acid δ-lactone; glucono delta lactone; delta gluconolactone; Fujiglucon. $C_6H_{10}O_6$; mol wt 178.14. C 40.45%, H 5.66%, O 53.89%. Prepn by oxidation of glucose with bromine water: Isbell, Pigman, *J. Res. Nat. Bur. Stand.* **10**, 337 (1933); by oxidation of glucose in *Acetobacter suboxydans:* King, Cheldelin, *Biochem. J.* **68**, 31P (1958). Structure: J. Stanék *et al., The Monosaccharides* (Academic Press, New York, 1963) p 271.



Crystals, dec 153°. Sweet taste (different from gluconic acid). $[\alpha]_D^{20}$ +61.7° (c = 1). Soly in water 59 g/100 ml; in alc about 1 g/100 g. Insol in ether. Hydrolyzed to gluconic acid by water. A freshly prepd 1% aq soln has a pH of 3.6 changing to pH 2.5 within 2 hrs.

USE: Component of many cleaning cmpds because of the sequestering ability of the gluconate radical which remains active in alk solns; in the dairy industry to prevent milkstone; in breweries to prevent beerstone; as latent acid catalyst for acid colloid resins, particularly in textile printing; as a coagulant for tofu.

4471. Glucosamine. [3416-24-8] 2-Amino-2-deoxy-D-glucose; chitosamine. $C_6H_{13}NO_5$; mol wt 179.17. C 40.22%, H 7.31%, N 7.82%, O 44.65%. Found in chitin, in mucoproteins, and in mucopolysaccharides. Isoln from chitin: Ledderhose, *Z. Physiol. Chem.* **2**, 213 (1878); Hackman, *Aust. J. Biol. Sci.* **7**, 168 (1954). Synthesis: Fischer, Leuchs, *Ber.* **35**, 3787 (1902); **36**, 24 (1903). Separation of α- and β-forms: Westphal, Holzmann, *ibid.* **75B**, 1274 (1942). Structure: Haworth *et al., J. Chem. Soc.* **1939**, 271; Cutler, Peat, *ibid.* 782; Cox, Jeffrey, *Nature* **143**, 894 (1939). Pharmacokinetics in dog and man: I.